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APPLICATION

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TITLE: ANALOGUES OF GLP-1

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ANALOGUES OF GLP-1

Cross-Reference to Related Applications

This application is a national phase application filed under 35 U.S.C. 371 of International Application No. PCT/EP99/09660, filed December 7, 1999, which claims the benefit of U.S. application No. 60/111,255, filed December 7, 1998, the contents of which are incorporated herein by reference.

Background of the Invention

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

Glucagon-like peptide-1 (7-36) amide (GLP-1) (SEQ ID NO:1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor preproglucagon (Varndell, J. M., et al., J. Histochem Cytochem, 1985:33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for a given rise in plasma glucose concentration, the increase in plasma insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., Lancet 1987:2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans. In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying (Wettergren A., et al., Dig Dis Sci 1993:38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D. A. et al., J. Clin Invest 1994:93:2293-6).

In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak, M. K., et al., Diabetes Care 1994:17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., J. Clin Endo Metab 1996:81:327-32). Unlike sulphonylureas, the

insulinotropic action of GLP-1 is dependent on plasma glucose concentration (Holz, G. G. 4th, et al., Nature 1993:361:362-5). Thus, the loss of GLP-l-mediated insulin release at low plasma glucose concentration protects against severe hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently influences glycemic levels as well as insulin and glucagon concentrations (Orskov, C, Diabetologia 35:701-711, 1992; Holst, J. J., et al., *Potential of GLP-1 in diabetes management* in Glucagon III, Handbook of Experimental Pharmacology, Lefevbre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii: 1300-1304, 1987; Weir, G. C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D. M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M. A., et al., Diagbetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W. O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogenously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

Summary of the Invention

In one aspect, the present invention is directed to a compound of formula (I),

(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 (SEQ ID NO:412),

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, β-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4- Pal, β-Nal, Cha, Trp or X^1-Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal or X^1-Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X^1-Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, β-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O) or NH-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O) or NH-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Phe, Pal, β- Nal, X^1-Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X^1-Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or X^1-Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O) or NH-CH($(CH_2)_e$-X^3)-C(O);

A^{35} is Gly, β-Ala, D-Ala, Gaba, Ava, NH-$(CH_2)_m$-C(O), Aib, Acc or a D-amino acid;

A^{36} is L-or D-Arg, D-or L-Lys, D-or L-hArg, D-or L-Orn, HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O), NH-CH($(CH_2)_e$-X^3)-C(O) or deleted;

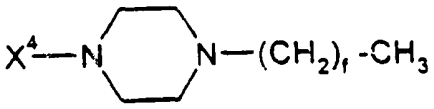
A^{37} is Gly, β-Ala, Gaba, Ava, Aib, Acc, Ado, Arg, Asp, Aun, Aec, NH-$(CH_2)_m$-C(O), HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O), a D-amino acid, or deleted;

A^{38} is D-or L-Lys, D-or L-Arg, D-or L-hArg, D-or L-Orn, HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O), NH-CH($(CH_2)_e$-X^3)-C(O), Ava, Ado, Aec or deleted;

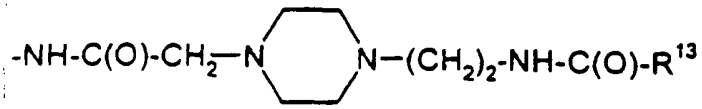
A^{39} is D-or L-Lys, D-or L-Arg, HN-CH($(CH_2)_n$-N(R^{10}-R^{11}))-C(O), Ava, Ado, or Aec;

X^1 for each occurrence is independently selected from the group consisting of (C_1-C_6)alkyl, OH and halo;

R^1 is OH, NH_2, (C_1-C_{30}) alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a (C_1-C_{12}) hydrocarbon moiety, and Z^0 is H, OH, CO_2H or $CONH_2$;

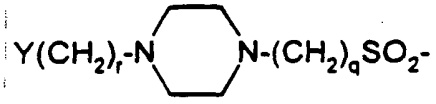


X^3 is

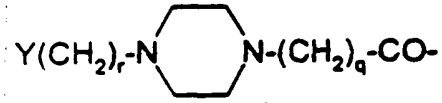


or -C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is , independently for each occurrence, an integer from 1 to 29 inclusive;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, and hydroxynaphthyl(C_1-C_{30})alkyl; or one of R^2 and R^3 is $(CH_3)_2$-N-$\overset{\uparrow}{C}$=$\overset{+}{N}(CH_3)_2$, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, C(O)X^5,



, or



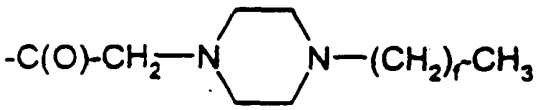
; wherein Y is H, OH or NH_2; r is 0 to 4; q is 0 to 4; and X^5 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl or hydroxynaphthyl(C_1-C_{30})alkyl;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

each of R^{10} and R^{11} is, independently for each occurrence, H, (C_1-C_{30})alkyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, -C((NH)(NH_2)) or



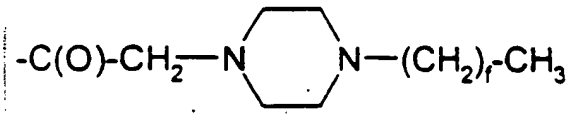
; and

R^{12} and R^{13} each is, independently for each occurrence, (C_1-C_{30})alkyl;

provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, -C((NH)(NH_2)) or



, then R^{11} is H or $(C_1\text{-}C_{30})$alkyl;

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH_2 or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not ($Arg^{26,34}$, Lys^{38})hGLP-1(7-38)-E, (Lys^{26}(N_ε-alkanoyl))hGLP-1(7-36, -37 or -38)-E, (Lys^{34}(N_ε-alkanoyl))hGLP-1(7-36, -37 or -38)-E, ($Lys^{26,34}$-bis(N_ε-alkanoyl))hGLP-1(7-36, -37 or -38)-E, (Arg^{26}, Lys^{34}(N_ε-alkanoyl))hGLP-1(8-36, -37 or -38)-E, ($Arg^{26,34}$, Lys^{36}(N_ε-alkanoyl))hGLP-1(7-36, -37 or -38)-E or ($Arg^{26,34}$, Lys^{38}(N_ε-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or -NH_2;

(iv) a compound of formula (I) is not Z^1-hGLP-1(7-36, -37 or -38)-OH, Z^1-hGLP-1(7-36, -37 or -38)-NH_2, wherein Z^1 is selected from the group consisting of:

(a) (Arg^{26}), (Arg^{34}), ($Arg^{26,34}$), (Lys^{36}), (Arg^{26}, Lys^{36}), (Arg^{34}, Lys^{36}), (D-Lys^{36}), (Arg^{36}), (D-Arg^{36}), ($Arg^{26,34}$, Lys^{36}) or ($Arg^{26,36}$, Lys^{34});

(b) (Asp^{21});

(c) at least one of (Aib^8), (D-Ala^8) and (Asp^9); and

(d) (Tyr^7), (N-acyl-His^7), (N-alkyl-His^7), (N-acyl-D-His^7) or (N-alkyl-D-His^7);

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not (N-Me-Ala^8)hGLP-1(8-36 or -37), (Glu^{15})hGLP-1(7-36 or -37), (Asp^{21})hGLP-1(7-36 or -37) or (Phe^{31})hGLP-1(7-36 or -37) or a pharmaceutically acceptable salt thereof.

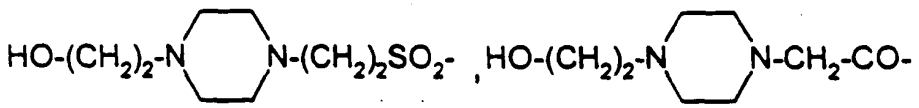
A preferred group of compounds of the immediately foregoing compound is where A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe or β-Nal; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where A^9 is Glu, N-Me-Glu or N-Met-Asp; A^{12} is Phe, Acc, β-Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr or β-Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O); A^{28} is Phe or β-Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

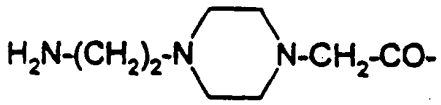
A preferred group of compounds of the immediately foregoing group of compounds is where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, β-Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, β-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, β-Ala, Ado, A6c, A5c, D-Arg or Gly; and A^{37} is Gly, Aib, β-Ala, Ado, D-Ala, Ava, Asp, Aun, D-Asp, D-Arg, Aec, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or deleted; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where X^4 for each occurrence is -C(O)-; and R^1 is OH or NH_2; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds or a pharmaceutically acceptable salt thereof is where R^2 is H and R^3 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl,

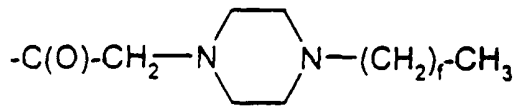


or



A preferred compound of the formula (I) is where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, β-Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, β-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, β-Ala, Ado, A6c, A5c, D-Arg or Gly; and A^{37} is Gly, Aib, β-Ala, Ado, D-Ala, Ava, Asp, Aun, D-Asp, D-

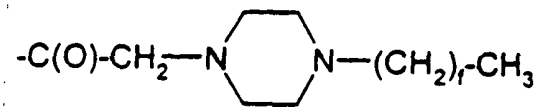
Arg, Aec, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH_2; R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl or



,

and R^{11} is H; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing compounds is where R^{10} is (C_4-C_{20})acyl, (C_4-C_{20})alklysulfonyl or



, or a

pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is of the formula:
($Aib^{8,35}$)hGLP-1(7-36)NH_2 (SEQ ID NO:2),
((N_α-HEPES-His)^7, $Aib^{8,35}$)hGLP-1(7-36)NH_2 (SEQ ID NO:3),
((N_α-HEPA-His)^7, $Aib^{8,35}$)hGLP-1(7-36)NH_2 (SEQ ID NO:4),
(Aib^8, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:5),
($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:6),
($Aib^{8,35}$, Arg^{26}, Lys^{34}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:7),
($Aib^{8,35,37}$, $Arg^{26,34}$, Lys^{38}(N_ε-tetradecanoyl))hGLP-1(7-38)NH_2 (SEQ ID NO:8),
($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:9),
($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-dodecanesulfonyl))hGLP-1(7-36)NH_2 (SEQ ID NO:10),
($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:11),
($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:12),
($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-tetradecylamino))hGLP-1(7-36)NH_2 (SEQ ID NO:13),
($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl),β-Ala^{37})hGLP-1(7-37)-OH (SEQ ID NO:14) or
($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N_ε-tetradecanoyl))hGLP-1(7-36)-OH (SEQ ID NO:15), or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:
($Aib^{8,35}$)hGLP-1(7-36)NH_2 (SEQ ID NO:2),

(Aib^{8}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:5),

(Aib^{8,35}, Arg^{26}, Lys^{34}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:7),

(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N_ε-tetradecanoyl))hGLP-1(7-38)NH_2 (SEQ ID NO:8),

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ε-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:9), or

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ε-tetradecanoyl), β-Ala^{37})hGLP-1(7-37)-OH (SEQ ID NO:14), or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) is where said compound is of the formula:

(Aib^{8,35}, A6c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:16);

(Aib^{8,35}, Glu^{23})hGLP-1(7-36)NH_2 (SEQ ID NO:17);

(Aib ^{8,24,35})hGLP-1(7-36)NH_2 (SEQ ID NO:18);

(Aib^{8,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:19);

(Aib^{8}, Glu^{23}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:20);

(Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH_2 (SEQ ID NO:21);

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^ε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:22);

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N^ε-decanoyl))hGLP-1(7-36)OH (SEQ ID NO:23);

(Aib^{8,35}, Lys^{25}, Arg^{26,34}Lys^{36}(N^ε-decanoyl))hGLP-1(7-36)OH (SEQ ID NO:24);

(Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{36}(N^ε-Aec-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:25);

(Aib^{8,35}, Arg^{26,34}, Ava^{37}, Ado^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:26);

(Aib^{8,35}, Arg^{26,34}, Asp^{37}, Ava^{38}, Ado^{39})hGLP-1(7-39)NH_2 (SEQ ID NO:27);

(Aib^{8,35}, Arg^{26,34}, Aun^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:28);

(Aib^{8,17,35})hGLP-1(7-36)NH_2 (SEQ ID NO:29);

(Aib^{8}, Arg^{26,34}, β-Ala^{35}, D-Asp^{37}, Ava^{38}, Aun^{39})hGLP-1(7-39)NH_2 (SEQ ID NO:30);

(Gly^{8}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:31);

(Ser^{8}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:32);

(Aib^{8}, Glu^{22,23}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:33);

(Gly^{8}, Aib^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:34);

(Aib^{8}, Lys^{18}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO: 35);

(Aib^{8}, Leu^{27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:36);

(Aib^{8}, Lys^{33}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:37);

(Aib^{8}, Lys^{18}, Leu^{27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:38);

(Aib^{8}, D-Arg^{36})hGLP-1(7-36)NH_2 (SEQ ID NO:39);

(Aib^{8}, β-Ala^{35}, D-Arg^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:40);

(Aib^{8,27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:41);

(Aib^{8,27}, β-Ala^{35,37}, Arg^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:42);

(Aib^{8,27}, β-Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH_2 (SEQ ID NO:43);

(Aib^{8}, Lys^{18,27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:44);

(Aib^{8}, Lys^{27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:45);

(Aib^{8}, β-Ala^{35}, Arg^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:46);

(Aib^{8}, Arg^{26,34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:47);

(Aib^{8}, D-Arg^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:48);

(Aib^{8}, β-Ala^{35}, Arg^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:49);

(Aib^{8}, Phe^{31}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:50);

(Aib^{8,35}, Phe^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:51);

(Aib^{8,35}, Nal^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:52);

(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH_2 (SEQ ID NO:53);

(Aib^{8,35}, Arg^{26,34}, Nal^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:54);

(Aib^{8,35}, Arg^{26,34}, Phe^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:55);

(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH_2 (SEQ ID NO:56);

(Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH_2 (SEQ ID NO:57);

(Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:58);

(Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:59);

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:60);

(Aib^{8}, β-Ala^{35}, Ser^{37}(O-decanoyl))hGLP-1(7-37)-NH_2 (SEQ ID NO:61);

(Aib^{8,27}, β-Ala^{35,37}, Arg^{38}, Lys^{39}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-39)NH_2 (SEQ ID NO:62);

(Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-37)NH_2 (SEQ ID NO:63);

(Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-37)NH_2 (SEQ ID NO:64); or

(Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-37)NH_2 (SEQ ID NO:65);

or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) is each of the compounds that are specifically enumerated hereinbelow in the Examples section of the present disclosure, or a pharmaceutically acceptable salt thereof.

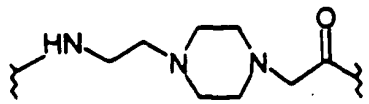
In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier of diluent.

In yet another aspect, the present invention provides a method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired, in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof. A preferred method of the immediately foregoing method is where the disease being treated is Type I diabetes or Type II diabetes.

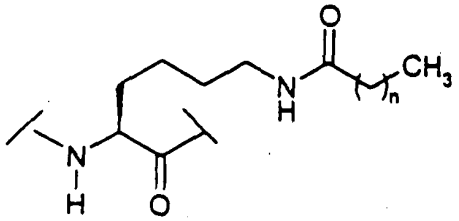
With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side chain of an amino acid (e.g., CH_3 for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R^2R^3)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R^2 and R^3 are as defined above, except when A^7 is Ura, Paa or Pta, in which case R^2 and R^3 are not present since Ura, Paa and Pta are considered here as des-amino amino acids. Amp, β-Nal, Nle, Cha, 3-Pal, 4-Pal and Aib are the abbreviations of the following α-amino acids: 4-amino-phenylalanine, β-(2-naphthyl)alanine, norleucine, cyclohexylalanine, β-(3-pyridinyl)alanine, β-(4-pyridinyl)alanine and α-aminoisobutyric acid, respectively. Other amino acid definitions are: Ura is urocanic acid; Pta is (4-pyridylthio) acetic acid; Paa is *trans*-3-(3-pyridyl) acrylic acid; Tma-His is N,N-tetramethylamidino-histidine; N-Me-Ala is N-methyl-alanine; N-Me-Gly is N-methyl-glycine; N-Me-Glu is N-methyl-glutamic acid; Tle is *tert*-butylglycine; Abu is α-aminobutyric acid; Tba is *tert*-butylalanine; Orn is ornithine; Aib is α-aminoisobutyric acid: β-Ala is β-alanine; Gaba is γ-aminobutyric acid; Ava is 5-aminovaleric acid; Ado is 12-aminododecanoic acid; Aic is 2-aminoindane-2-carboxylic acid; Aun is 11-aminoundecanoic

acid; and Aec is 4-(2-aminoethyl)-1-carboxymethyl-piperazine, represented by the structure:

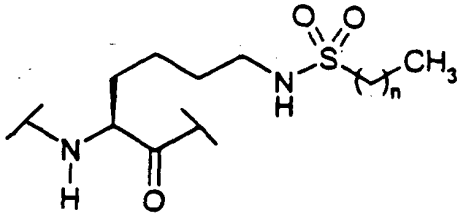


What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid (A3c); 1-amino-1-cyclobutanecarboxylic acid (A4c); 1-amino-1-cyclopentanecarboxylic acid (A5c); 1-amino-1-cyclohexanecarboxylic acid (A6c); 1-amino-1-cycloheptanecarboxylic acid (A7c); 1-amino-1-cyclooctanecarboxylic acid (A8c); and 1-amino-1-cyclononanecarboxylic acid (A9c). In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX^5 stands for $-C{=}O{\cdot}X^5$. Examples of $-C{=}O{\cdot}X^5$ include, but are not limited to, acetyl and phenylpropionyl.

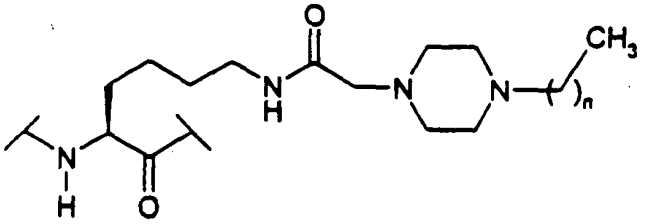
What is meant by Lys(N_ε-alkanoyl) is represented by the following structure:



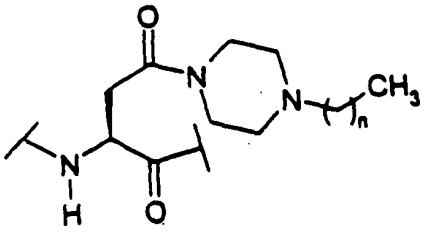
. What is meant by Lys(N_ε-alkylsulfonyl) is represented by the following structure:



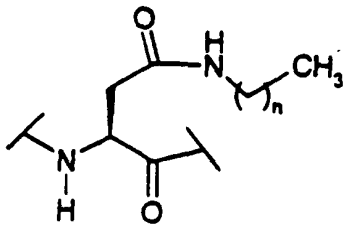
. What is meant by Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following structure:



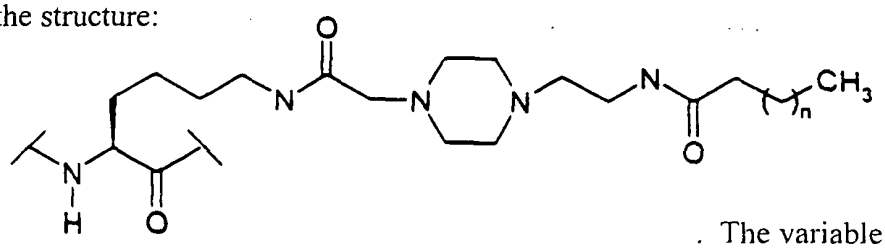
. What is meant by Asp(1-(4-alkyl-piperazine)) is represented by the following structure:



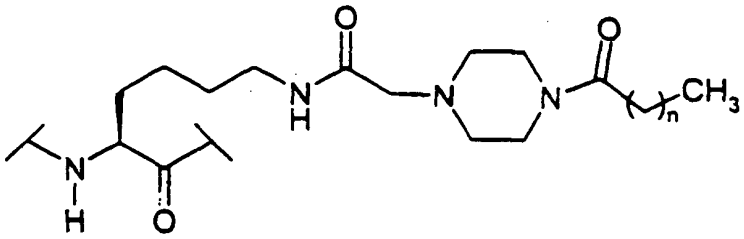
What is meant by Asp(1-alkylamino) is represented by the following structure:



. What is meant by Lys(N_ε-Aec-alkanoyl) is represented by the structure:



. The variable n in the foregoing structures is 1-30. What is meant by Lys (Nε-ace-alkanoyl) is represented by the structure:



The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2CIZ for 2-chlorobenzyloxycarbonyl, 2BrZ for 2-bromobenzyloxycarbonyl, OcHex for O-cyclohexyl, Fmoc for 9-fluorenylmethoxycarbonyl, HOBt for N-hydroxybenzotriazole and PAM resin for 4-hydroxymethylphenylacetamidomethyl resin.

The term "halo" encompasses fluoro, chloro, bromo and iodo.

The term "(C_1-C_{30})hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl, and in the case of alkenyl and alkynyl there are C_2-C_{30}.

A peptide of this invention is also denoted herein by another format, e.g., (A5c^8)hGLP-1(7-36)NH_2 (SEQ ID NO:66), with the substituted amino acids from the natural sequence placed between the set of parentheses (e.g., A5c^8 for Ala^8 in hGLP-1). The abbreviation GLP-1 means glucagon-like peptide-1; hGLP-1 means human glucagon-like peptide-1. The numbers between

the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) (SEQ ID NO:1) is amino acids 7 through 36 of the peptide sequence for human GLP-1). The sequence for hGLP-1(7-37) (SEQ ID NO:413) is listed in Mojsov, S., Int. J. Peptide Protein Res,. 40, 1992, pp. 333-342. The designation "NH_2" in hGLP-1(7-36)NH_2 (SEQ ID NO:1) indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) (SEQ ID NO:1) means that the C-terminus is the free acid. In hGLP-1(7-38) (SEQ ID NO:414), residues in positions 37 and 38 are Gly and Arg, respectively.

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R^2 and R^3 of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, may be attached using reductive alkylation. Hydroxylalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE^1, may be attached by coupling the free acid, e.g., E^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R^1 is NH-X^2-CH_2-$CONH_2$, (i.e., Z^0=$CONH_2$), the synthesis of the peptide starts with Boc-HN-X^2-CH_2-COOH which is coupled to the MBHA resin. If R^1 is NH-X^2-CH_2-COOH, (i.e., Z^0=COOH) the synthesis of the peptide starts with Boc-HN-X^2-CH_2-COOH which is coupled to the PAM resin. For this particular step, 4 molar equivalents of Boc-HN-X^2-COOH, HBTU and HOBt and 10 molar equivalents of DIEA are used. The coupling time is about 8 hours.

The protected amino acid 1-(N-tert-butoxycarbonyl-amino)-1-cyclohexane-carboxylic acid (Boc-A6c-OH) was synthesized as follows. 19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 ml of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this

solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous later was adjusted to about 3 by adding 4N HCl. The organic layer was separated. The aqueous later was extracted with ethyl acetate (1 x 100 ml). The two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of the pure product was obtained. 29% yield.

Boc-A5c-OH was synthesized in an analogous manner to that of Boc-A6c-OH. Other protected Acc amino acids can be prepared in an analogous manner by a person of ordinary skill in the art as enabled by the teachings herein.

In the synthesis of a GLP-1 analogue of this invention containing A5c, A6c and/or Aib, the coupling time is 2 hrs. for these residues and the residue immediately following them. For the synthesis of (Tma-His^7)hGLP-1(7-36)NH_2 (SEQ ID NO:67), HBTU (2 mmol) and DIEA (1.0 ml) in 4 ml DMF are used to react with the N-terminal free amine of the peptide-resin in the last coupling reaction; the coupling time is about 2 hours.

The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, can be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX^1, can be attached by coupling the free acid, e.g., X^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., ρ-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's

medium (DMEM) containing 10% fetal calf serum, and maintained at about 37 °C in a humidified atmosphere of 5% CO_2/95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10 min), and the final pellets were resuspended in 50 mM Tris-HCl, containing 2.5 mM $MgCl_2$, 0.1 mg/ml bacitracin (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM (^{125}I)GLP-1(7-36) (SEQ ID NO:415) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound (^{125}I)GLP-1(7-36) (SEQ ID NO:415) was separated from the free by rapid filtration through GF/C filters (Brandel, Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total (^{125}I)GLP-1(7-36) (SEQ ID NO:415) bound minus that bound in the presence of 1000 nM GLP-1(7-36) (SEQ ID NO:1) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow

rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous (See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536). Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis, neurodegenerative diseases, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired. GLP-1 analogous of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied: however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of $1x10^{-7}$ to 200 mg/kg/day, preferably $1x10^{-4}$ to 100 mg/kg/day, which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intraveneous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert

pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January

29, 1998, teaches absorbable sustained release compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and application are incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

Boc-βAla-OH, Boc-D-Arg(Tos)-OH and Boc-D-Asp(OcHex) were purchased from Nova Biochem, San Diego, California. Boc-Aun-OH was purchased from Bachem, King of Prussia, PA. Boc-Ava-OH and Boc-Ado-OH were purchased from Chem-Implex International, Wood Dale, IL. Boc-Nal-OH was purchased from Synthetech, Inc. Albany, OR.

Example 1

$(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:2)

The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnolzer, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-methylbenz-hydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.91 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The synthesis was carried out on a 0.20 mmol

scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min. except for the Boc-Aib-OH residues and the following residues, Boc-Lys(2ClZ)-OH and Boc-His(DNP)-OH wherein the coupling times were 2 hours.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side chain of Trp was removed by treatment with a a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C_{18} column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (20% to 50% of solution B over 105 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of FTA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 135 mg of a white solid was obtained. Purity was 98.6% based on analytical HPLC analysis. Electro-spray mass spectrometer (MS(ES))S analysis gave the molecular weight at 3339.7 (in agreement with the calculated molecular weight of 3339.7).

Example 2

$((N_{\alpha}\text{-HEPES-His})^{7}, Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:3)

The title compound (HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)) can be synthesized as follows: after assembly of the peptide $(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:2) on MBHA resin (0.20 mmol) according to the procedure of Example 1, the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for 2 min. After washing with DMF and DCM, the resin is

treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group on the His side chain and formyl group on the Trp side chain as described above before the final HF cleavage of the peptide from the resin.

Example 3

(N_α-HEPA-His)^7, Aib^{8,35})hGLP-1(7-36)NH_2 (SEQ ID NO:4)

The title compound (HEPA is (4-(2-hydroxyethyl)-1-piperazineacetyl)) can be made substantially according to the procedure described in Example 2 for making ((N_α-HEPES-His)^7, Aib^{8,35})hGLP-1(7-36)NH_2 (SEQ ID NO:3) except that 2-bromoacetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

Example 4

(Aib^8, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:5)

The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids. MS (ES) = 3325.7, calculated MW = 3325.8, purity = 99%, yield = 85 mg.

The synthesis of other compounds of the present invention can be accomplished in substantially the same manner as the procedure described for the synthesis of (Aib^{8,35})hGLP-1(7-36)NH_2 (SEQ ID NO:2) in Example 1 above, but using the appropriate protected amino acids depending on the desired peptide.

Example 5

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_ε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:6)

The Boc amino acids used were the same as those in the synthesis of (Aib^{8,35})hGLP-1(7-36)NH_2 (SEQ ID NO:2) described in Example 1 except that Fmoc-Lys(Boc)-OH was used in this example. The first amino acid residue was coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH was dissolved in 4 mL of 0.5N HBTU in DMF. To the solution was added 1 mL of DIEA. The mixture was shaken for about 2 min. To the solution was then added 0.2 mmol of MBHA resin (substitution = 0.91 mmol/g). The mixture was shaken for about 1 hr. The resin was washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin was washed with DMF. Myristic acid (2.5 mmol) was pre-activated with HBTU

(2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF for 2 min and was coupled to the Fmoc-Lys-resin. The coupling time was about 1 hr. The resin was washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin was washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The following steps synthesis and purification procedures for the peptide were the same as those in the synthesis of $(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:2) in Example 1. 43.1 mg of the title compound were obtained as a white solid. Purity was 98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3577.7 in agreement with the calculated molecular weight 3578.7.

Example 6-8

Examples 6-8 were synthesized substantially according to the procedure described for Example 5 using the appropriate protected amino acid and the appropriate acid in place of the Myristic acid used in Example 5.

Example 6: $(Aib^{8,35}, Arg^{26}, Lys^{34}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:7); Yield = 89.6 mg; MS(ES) = 3577.2, Calculated MW = 3578.7; Purity 96%.

Example 7: $(Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}38)NH_2$ (SEQ ID NO:8); Yield = 63.3 mg; MS(ES) = 3818.7; Calculated MW = 3819.5; Purity 96%.

Example 8: $(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-decanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:9); Yield = 57.4 mg; MS(ES) = 3521.5; Calculated MW = 3522.7; Purity 98%; Acid = decanoic acid.

The syntheses of the other compounds of the present invention containing $Lys(N_\varepsilon$-alkanoyl) residue can be carried out in an analogous manner to the procedure described for Example 5, $(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N_\varepsilon\text{-tetradecanoyl}))hGLP\text{-}1(7\text{-}36)NH_2$ (SEQ ID NO:6). Fmoc-Lys(Boc)-OH amino acid is used for the residue of $Lys(N_\varepsilon$-alkanoyl) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys. If the $Lys(N_\varepsilon$-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the $Lys(N_\varepsilon$-alkanoyl) residue is assembled on the resin on the peptide synthetizer first. The appropriate acid corresponding to the desired alkanoyl can be purchased from Aldrich Chemical Co., Inc. Milwaukee, WI, USA, e.g., octanoic acid, decanoic acid, lauric acid and palmitic acid.

Example 9

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$_\varepsilon$-dodecanesulfonyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:10)

The Boc amino acids to be used in this synthesis are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin (substitution = 0.91 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF and to it is added 0.25 mmol of 1-dodecanesulfonyl chloride in 4 mL of DMF and 1 mL of DIEA. The mixture is shaken for about 2 hrs. The resin is washed with DMF and treated with 25% piperidine in DMF for 2 x 20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The synthesis of the rest of the peptide and purification procedures are the same as those described in Example 1.

The syntheses of other compounds of the present invention containing Lys(N$_\varepsilon$-alkylsulfonyl) residue can be carried out in an analogous manner to the procedure described in Example 9. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N$_\varepsilon$-alkylsulfonyl) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys. If the Lys(N$_\varepsilon$-alkylsulfonyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N$_\varepsilon$-alkylsulfonyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate akylsulfonyl chloride can be obtained from Lancaster Synthesis Inc., Windham, NH, USA, e.g., 1-octanesulfonyl chloride, 1-decanesulfonyl chloride, 1-dodecanesulfonyl chloride, 1-hexadecanesulfonyl chloride and 1-octadecylsulfonyl chloride.

Example 10

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$_\varepsilon$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH$_2$ (SEQ ID NO:11)

The Boc amino acids to be used for this example are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then

added 0.2 mmol of MBHA (substitution = 0.91 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF. The 2-bromoacetic acid (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1 mL) in 4 mL of DMF for about 2 min and is added to the resin. The mixture is shaken for about 10 min and washed with DMF. The resin is then treated with 1.2 mmol of piperazine in 4 mL of DMF for about 2 hrs. The resin is washed with DMF and treated with 2 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as the procedures described for Example 1.

The syntheses of other compounds of the present invention containing Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 10. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys. The corresponding iodoalkane is used for the residue of Lys(N_ε-(2-(4-alky-1-piperazine)-acetyl)) during the alkylation step. If the Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is assembled on the resin on the peptide synthesizer first.

Example 11

($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:12)

The Boc amino acids to be used in this example are the same as the amino acids used in synthesis of Example 5 except Fmoc-Asp(O-tBu)-OH is used at position 36. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the tBu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min.

0.6 mmol of piperazine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 3 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as those for the synthesis of Example 1.

The syntheses of other compounds of the present invention comprising Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 11. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu. The corresponding iodoalkane is used for the residue of Lys(N_ε(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is assembled on the resin on the peptide synthesizer first.

Example 12

($Aib^{8,35}$, $Arg^{26,34}$, Asp^{36}(1-tetradecylamino))hGLP-1(7-36)NH_2 (SEQ ID NO:13)

The Boc amino acids to be used for this example are the same as those used in Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the t-Bu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL)in 4 mL of DMF for about 15 min. 0.6 mmol of 1-tetradecaneamine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the

synthesis. The remaining synthesis and purification procedures for the peptide of this example are the same as those described for the synthesis of Example 1.

The syntheses of other compounds of the present invention containing Asp(1-alkylamino) or Glu(1-alkylamino) residue are carried out in an analogous manner as described for the synthesis of Example 12. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-alkylamino) or Glu(1-alkylamino), respectively, in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu, respectively. If the Asp(1-alkylamino) or Glu(1-alkylamino) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-alkylamino) or Glu(1-alkylamino) residue is assembled on the resin on the peptide synthesizer first.

Example 13

($Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N_\varepsilon$-tetradecanoyl),β-Ala^{37})hGLP-1(7-37)-OH (SEQ ID NO:14)

The Boc amino acids used are the same as those in the synthesis of ($Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N_\varepsilon$-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:6) (Example 5). 270 mg of Boc-β-Ala-PAM resin (Novabiochem, San Diego, California, substitution=0.74 mmol/g) was used. The Boc protecting group on Boc-β-Ala-PAM resin was deblocked on a shaker with 100%TFA for 2x2 min first. The remainder of the synthesis and purification procedures were the same as that in Example 5. 83.0 mg of the title peptide was obtained as white solid. Purity was 99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3650.5 in agreement with the calculated weight 3650.8.

Example 14

($Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N_\varepsilon$-tetradecanoyl))hGLP-1(7-36)-OH (SEQ ID NO:15)

The Boc amino acids to be used are the same as those in the synthesis of ($Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N_\varepsilon$-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:6) (Example 5). Fmoc-Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOBt (2.0 mmol) and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures are the same as those in Example 5. Electro-spray mass spectrometer analysis gave the molecular weight at 3579.15 in agreement with the calculated weight 3579.5.

The synthesis of other analogs of hGLP-1(7-36)-OH (SEQ ID NO:1), hGLP-1(7-37)-OH (SEQ ID NO:413) and hGLP-1(7-38)-OH (SEQ ID NO:414) of the instant invention which contain Lys(N_ε(alkanoyl) residue can be carried out in an analogous manner according to the procedure described for the synthesis of Example 14. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε(alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys.

Example 366

(Aib^8, β-Ala^{35}, Aec^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:68)

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-OH (0.40g, 0.829 mmol), HBTU (1.5 mL @ 0.5M in DMF) and DIEA (0.5mL) in a reaction vessel was shaken on a shaker for 4h at room temperature. The resin was then washed with DMF and treated with 25% piperidine in DMF for 2x20min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spry mass spectrometer analysis gave the molecular weight at 3494.8 in agreement with the calculated molecular weight 3494.99. Purity 93%; Yield 79.1mg.

Example 367

(Aib^8, β-Ala^{35}, Aec^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:69)

Example 367 was synthesized substantially according to the procedure described for Example 366. MS(ES)=3551.7, calculated MW=3552.04; Purity 97%; Yield 97.4mg.

Example 368

(Aib^8, β-Ala^{35}, $Aec^{37,38}$) hGLP-1(7-38)NH_2 (SEQ ID NO:70)

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL) in a reaction vessel was shaken on a shaker for 2h at room temperature. The resin was then washed with DMF and treated with 30% piperidine in DMF for 2x15min. The resin as washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 2h. The resin was

washed with DMF and treated with 30% piperidine in DMF for 2x15min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Elecro-spry mass spectrometer analysis gave the molecular weight at 3663.9 in agreement with the calculated molecular weight 3664.26. Purity 100%; Yield 75.3mg.

Example 369

(Aib^{8}, $Arg^{26,34}$, β-Ala^{35}, Lys^{36}(N^{ε}-Aec-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:25)

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Boc-Lys(Fmoc)-OH (1.17g, 2.5mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) in a reaction vessel was shaken on a shaker at room temperature for 10min. The resin was washed with DMF and treated with 25% piperidine in DMF for 2x15min. The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 10min. The resin was washed with DMF and treated with 30% piperidine in DMF for 2x15min. The resin was washed with DMF and treated with a mixture of decanoic acid (431mg, 2.5mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) for 10 min. The resin was washed with DMF and treated with 100% TFA for 2x2 min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Elecro-spry mass spectrometer analysis gave the molecular weight at 3677.0 in agreement with the calculated molecular weight 3677.25. Purity 97.6%; Yield 44.8mg.

The following examples can be made according to the appropriate procedures described hereinabove.

Example 15: (Aib^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:71)

Example 16: (β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:72)

Example 17: ((N^{α}-Me-His)^{7}, $Aib^{8,35}$)hGLP-1(7-36)NH_2 (SEQ ID NO:73)

Example 18: ((N^{α}-Me-His)^{7}, Aib^{8}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:74)

Example 19: ((N^{α}-Me-His)^{7}, $Aib^{8,35}$, $Arg^{26,34}$)hGLP-1(7-36)NH_2 (SEQ ID NO:75)

Example 20: ((N^{α}-Me-His)^{7}, Aib^{8}, $Arg^{26,34}$, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:76)

Example 21: (Aib^{8}, $A6c^{35}$)hGLP-1(7-36)NH_2 (SEQ ID NO:77)

Example 22: (Aib^{8}, A5c^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:78)

Example 23: (Aib^{8}, D-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:79)

Example 24: (Aib^{8,35}, A6c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:16)

Example 25: (Aib^{8,35}, A5c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:80)

Example 26: (Aib^{8,35}, Glu^{23})hGLP-1(7-36)NH_2 (SEQ ID NO:17)

Example 27: (Aib ^{8,24,35})hGLP-1(7-36)NH_2 (SEQ ID NO:18)

Example 28: (Aib ^{8,30,35})hGLP-1(7-36)NH_2 (SEQ ID NO:81)

Example 29: (Aib ^{8,25,35})hGLP-1(7-36)NH_2 (SEQ ID NO:82)

Example 30: (Aib^{8,35}, A6c^{16,20})hGLP-1(7-36)NH_2 (SEQ ID NO:83)

Example 31: (Aib^{8,35}, A6c^{16,29,32})hGLP-1(7-36)NH_2 (SEQ ID NO:84)

Example 32: (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH_2 (SEQ ID NO:85)

Example 33: (Aib^{8,35}, A6c^{20})hGLP-1(7-36)NH_2 (SEQ ID NO:86)

Example 34: (Aib^{8,35}, Lys^{25})hGLP-1(7-36)NH_2 (SEQ ID NO:87)

Example 35: (Aib^{8,24,35}, A6c^{20})hGLP-1(7-36)NH_2 (SEQ ID NO:88)

Example 36: (Aib^{8,35}, A6c^{29,32})hGLP-1(7-36)NH_2 (SEQ ID NO:89)

Example 37: (Aib^{8,24,35}, A6c^{29,32})hGLP-1(7-36)NH_2 (SEQ ID NO:90)

Example 38: (Aib^{8,35}, A6c^{12})hGLP-1(7-36)NH_2 (SEQ ID NO:91)

Example 39: (Aib^{8,35}, Cha^{20})hGLP-1(7-36)NH_2 (SEQ ID NO:92)

Example 40: (Aib^{8,35}, A6c^{33})hGLP-1(7-36)NH_2 (SEQ ID NO:93)

Example 41: (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH_2 (SEQ ID NO:85)

Example 42: (Aib^{8}, A6c^{16,20}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:94)

Example 43: (Aib^{8,35}, β-Ala^{22})hGLP-1(7-36)NH_2 (SEQ ID NO:95)

Example 44: (Aib^{8,22,35})hGLP-1(7-36)NH_2 (SEQ ID NO:96)

Example 45: (Aib^{8,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:19)

Example 46: (Aib^{8,24,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:97)

Example 47: (Aib^{8,24,25,35}, Glu^{23}, A6c^{32})hGLP-1(7-36)NH_2 (SEQ ID NO:98)

Example 48: (Aib^{8,24,25,35}, A6c^{16,20,32}, Glu^{23},)hGLP-1(7-36)NH_2 (SEQ ID NO:99)

Example 49: (Aib^{8}, A6c^{32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:100)

Example 50: (Aib^{8}, A5c^{32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:101)

Example 51: (Aib^{8}, Glu^{23}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:20)

Example 52: (Aib^{8,24}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:102)

Example 53: (Aib^{8,30}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:103)

Example 54: (Aib^{8,25}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:104)

Example 55: (Aib^{8}, A6c^{16,20}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:94)

Example 56: (Aib^{8}, A6c^{16,29,32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:105)

Example 57: (Aib^{8}, A6c^{20,32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:106)

Example 58: (Aib^{8}, A6c^{20}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:107)

Example 59: (Aib^{8}, Lys^{25}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:108)

Example 60: (Aib^{8,24}, A6c^{20}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:109)

Example 61: (Aib^{8}, A6c^{29,32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:110)

Example 62: (Aib^{8,24}, A6c^{29,32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:111)

Example 63: (Aib^{8}, A6c^{12}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:112)

Example 64: (Aib^{8}, Cha^{20}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:113)

Example 65: (Aib^{8}, A6c^{33}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:114)

Example 66: (Aib^{8}, A6c^{20,32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:106)

Example 67: (Aib^{8}, β-Ala^{22,35})hGLP-1(7-36)NH_2 (SEQ ID NO:115)

Example 68: (Aib^{8,22}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:116)

Example 69: (Aib^{8}, Glu^{23}, A6c^{32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:117)

Example 70: (Aib^{8,24}, Glu^{23}, A6c^{32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:118)

Example 71: (Aib^{8,24}, Glu^{23}, A6c^{32}, Lys^{34}(N_ε-octanoyl), β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:119)

Example 72: (Aib^{8,24,25}, Glu^{23}, A6c^{32}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:120)

Example 73: (Aib^{8,24,25}, A6c^{16,20,32}, Glu^{23}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:121)

Example 74: (Aib^{8,35}, D-Arg^{36})hGLP-1(7-36)NH_2 (SEQ ID NO:122)

Example 75: (Aib^{8,35}, D-Lys^{36})hGLP-1(7-36)NH_2 (SEQ ID NO:123)

Example 76: (Aib^{8}, β-Ala^{35}, D-Arg^{36})hGLP-1(7-36)NH_2 (SEQ ID NO:124)

Example 77: (Aib^{8}, β-Ala^{35}, D-Lys^{36})hGLP-1(7-36)NH_2 (SEQ ID NO:125)

Example 78: (Aib^{8,35}, Arg^{26,34},)hGLP-1(7-36)NH_2 (SEQ ID NO:21)

Example 79: (Aib^{8}, Arg^{26,34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:126)

Example 80: (Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH_2 (SEQ ID NO:127)

Example 81: (Aib^{8}, Arg^{25,26,34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:128)

Example 82: (Aib[8], Arg[26,34], β-Ala[35], Lys[36](Nε-tetradecanoyl))hGLP-1(7-36)OH (SEQ ID NO:129)

Example 83: (Aib[8,35], Arg[26,34], Lys[36](Nε-tetradecanoyl))hGLP-1(7-37)OH (SEQ ID NO:130)

Example 84: (Aib[8,35,37], Arg[26,34], Lys[36](Nε-tetradecanoyl))hGLP-1(7-37)OH (SEQ ID NO:131)

Example 85: (Aib[8,35], Arg[26,34], Lys[36](Nε-tetradecanoyl), D-Ala[37])hGLP-1(7-37)OH (SEQ ID NO:132)

Example 86: (Aib[8,35,37], Arg[26,34], Lys[38](Nε-tetradecanoyl))hGLP-1(7-38)OH (SEQ ID NO:133)

Example 87: (Aib[8,35], Arg[26,34], β-Ala[37], Lys[38](Nε-tetradecanoyl))hGLP-1(7-38)OH (SEQ ID NO:134)

Example 88: (Aib[8,35], Arg[26,34], Lys[38](Nε-tetradecanoyl))hGLP-1(7-38)OH (SEQ ID NO:135)

Example 89: (Aib[8], Arg[26,34], Lys[36](Nε-tetradecanoyl), β-Ala[37])hGLP-1(7-37)OH (SEQ ID NO:136)

Example 90: (Aib[8,37], Arg[26,34], Lys[36](Nε-tetradecanoyl))hGLP-1(7-37)OH (SEQ ID NO:137)

Example 91: (Aib[8,35], Arg[26,34], Ado[37])hGLP-1(7-37)OH (SEQ ID NO:138)

Example 92: (Aib[8,35], Arg[26,34], Ado[37])hGLP-1(7-37)NH_2 (SEQ ID NO:139)

Example 93: (Aib[8], Arg[26,34], Lys[36](Nε-tetradecanoyl), D-Ala[37])hGLP-1(7-37)OH (SEQ ID NO 140)

Example 94: (Aib[8,37], Arg[26,34], Lys[38](Nε-tetradecanoyl))hGLP-1(7-38)OH (SEQ ID NO:141)

Example 95: (Aib[8], Arg[26,34], β-Ala[37], Lys[38](Nε-tetradecanoyl))hGLP-1(7-38)OH (SEQ ID NO:142)

Example 96: (Aib[8,35], Lys[26](Nε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:143)

Example 97: (Aib[8,35], Lys[26](Nε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:144)

Example 98: (Aib[8,35], Lys[26](Nε-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:145)

Example 99: (Aib[8], Lys[26](Nε-octanoyl), β-Ala[35])hGLP-1(7-36)NH_2 (SEQ ID NO:146)

Example 100: (Aib[8], Lys[26](Nε-tetradecanoyl), β-Ala[35])hGLP-1(7-36)NH_2 (SEQ ID NO:147)

Example 101: (Aib[8], Lys[26](Nε-hexadecanoyl), β-Ala[35])hGLP-1(7-36)NH_2 (SEQ ID NO:148)

Example 102: (Aib[8,35], Lys[26](Nε-octanoyl), Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:149)

Example 103: (Aib[8,35], Lys[26](Nε-tetradecanoyl), Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:150)

Example 104: (Aib[8,35], Lys[26](Nε-hexadecanoyl), Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:151)

Example 105: (Aib[8,35], Lys[26](Nε-decanoyl), Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:152)

Example 106: (Aib[8,35], Lys[25], Lys[26](Nε-octanoyl), Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:153)

Example 107: ($Aib^{8,35}$, Lys^{25}, Lys^{26}(N^{ε}-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH_2 (SEQ ID NO:154)

Example 108: ($Aib^{8,35}$, Lys^{25}, Lys^{26}(N^{ε}-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH_2 (SEQ ID NO:155)

Example 109: ($Aib^{8,35}$, $Arg^{25,34}$, Lys^{26}(N^{ε}-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:156)

Example 110: ($Aib^{8,35}$, $Arg^{25,34}$, Lys^{26}(N^{ε}-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:157)

Example 111: ($Aib^{8,35}$, $Arg^{25,34}$, Lys^{26}(N^{ε}-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:158)

Example 112: ($Aib^{8,35}$, $Arg^{25,34}$, Lys^{26}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:159)

Example 113: (Aib^{8}, Lys^{26}(N^{ε}-octanoyl), Arg^{34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:160)

Example 114: (Aib^{8}, Lys^{26}(N^{ε}-tetradecanoyl), Arg^{34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:161)

Example 115: (Aib^{8}, Lys^{26}(N^{ε}-hexadecanoyl), Arg^{34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:162)

Example 116: (Aib^{8}, Lys^{26}(N^{ε}-decanoyl), Arg^{34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:163)

Example 117: ($Aib^{8,35}$, Lys^{34}(N^{ε}-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:164)

Example 118: ($Aib^{8,35}$, Lys^{34}(N^{ε}-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:165)

Example 119: ($Aib^{8,35}$, Lys^{34}(N^{ε}-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:166)

Example 120: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:167)

Example 121: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:168)

Example 122: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:169)

Example 123: ($Aib^{8,35}$, $Arg^{25,26}$, Lys^{34}(N^{ε}-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:170)

Example 124: ($Aib^{8,35}$, $Arg^{25,26}$, Lys^{34}(N^{ε}-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:171)

Example 125: ($Aib^{8,35}$, $Arg^{25,26}$, Lys^{34}(N^{ε}-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:172)

Example 126: ($Aib^{8,35}$, $Arg^{25,26}$, Lys^{34}(N^{ε}-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:173)

Example 127: ($Aib^{8,35}$, Lys^{25}, Arg^{26}, Lys^{34}(N^{ε}-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:174)

Example 128: ($Aib^{8,35}$, Lys^{25}, Arg^{26}, Lys^{34}(N^{ε}-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:175)

Example 129: ($Aib^{8,35}$, Lys^{25}, Arg^{26}, Lys^{34}(N^{ε}-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:176)

Example 130: ($Aib^{8,35}$, Lys^{36}(N^{ε}-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:177)

Example 131: ($Aib^{8,35}$, Lys^{36}(N^{ε}-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:178)

Example 132: (Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:179)

Example 133: (Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:180)

Example 134: (Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:181)

Example 135: (Aib^{8,35}, Arg^{26}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:182)

Example 136: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:183)

Example 137: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:184)

Example 138: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:185)

Example 139: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:186)

Example 140: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:187)

Example 141: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:188)

Example 142: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:189)

Example 143: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:190)

Example 144: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:191)

Example 145: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:192)

Example 146: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:193)

Example 147: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:194)

Example 148: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:195)

Example 149: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:189)

Example 150: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:190)

Example 151: (Aib^{8,35,37}, Arg2^{5,26,34}, Lys^{38}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:191)

Example 152: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-38)NH$_2$ (SEQ ID NO:192)

Example 153: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:196)

Example 154: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:197)

Example 155: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:198)

Example 156: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:199)

Example 157: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:200)

Example 158: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:201)

Example 159: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:202)

Example 160: (Aib^{8}, Lys^{34}(N$^{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:203)

Example 161: (Aib^{8}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:204)

Example 162: (Aib^{8}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:205)

Example 163: (Aib^{8}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:206)

Example 164: (Aib^{8}, Glu^{23}, Lys^{34}(N$_{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:207)

Example 165: (Aib^{8}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:208)

Example 166: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:209)

Example 167: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:210)

Example 168: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:211)

Example 169: (Aib^{8}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-decanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:212)

Example 170: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:213)

Example 171: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:214)

Example 172: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:215)

Example 173: (Aib^{8}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-decanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:216)

Example 174: (Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:217)

Example 175: (Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:218)

Example 176: (Aib^{8}, Lys^{25}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl), β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:219)

Example 177: (Aib^{8}, β-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:220)

Example 178: (Aib^{8}, β-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:221)

Example 179: (Aib^{8}, β-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:222)

Example 180: (Aib[8], Arg[26], β-Ala[35], Lys[36](Nε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:223)

Example 181: (Aib[8], Arg[26], β-Ala[35], Lys[36](Nε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:224)

Example 182: (Aib[8], Arg[26], β-Ala[35], Lys[36](Nε-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:225)

Example 183: (Aib[8], Arg[26,34], β-Ala[35], Lys[36](Nε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:226)

Example 184: (Aib[8], Arg[26,34], β-Ala[35], Lys[36](Nε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:227)

Example 185: (Aib[8], Arg[26,34], β-Ala[35], Lys[36](Nε-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:228)

Example 186: (Aib[8], Arg[26,34], β-Ala[35], Lys[36](Nε-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:229)

Example 187: (Aib[8], Lys[25], Arg[26,34], β-Ala[35], Lys[36](Nε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:230)

Example 188: (Aib[8], Lys[25], Arg[26,34], Lys[36](Nε-tetradecanoyl), β-Ala[35])hGLP-1(7-36)NH_2 (SEQ ID NO:231)

Example 189: (Aib[8], Lys[25], Arg[26,34], β-Ala[35], Lys[36](Nε-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:232)

Example 190: (Aib[8], Arg[25,26,34], β-Ala[35], Lys[36](Nε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:233)

Example 191: (Aib[8], Arg[25,26,34], β-Ala[35], Lys[36](Nε-tetradecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:234)

Example 192: (Aib[8], Arg[25,26,34], β-Ala[35], Lys[36](Nε-hexadecanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:235)

Example 193: (Aib[8], Arg[25,26,34], β-Ala[35], Lys[36](Nε-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:236)

Example 194: (Aib[8,35], Lys[26](Nε-octanoyl), A6c[32], Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:237)

Example 195: (Aib[8,35], Lys[26](Nε-tetradecanoyl), A6c[32], Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:238)

Example 196: (Aib[8,35], Lys[26](Nε-hexadecanoyl), A6c[32], Arg[34])hGLP-1(7-36)NH_2 (SEQ ID NO:239)

Example 197: (Aib[8,35], A6c[32], Lys[34](Nε-octanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:240)

Example 198: (Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:241)

Example 199: (Aib^{8,35}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:242)

Example 200: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:243)

Example 201: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:244)

Example 202: (Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:245)

Example 203: (Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:246)

Example 204: (Aib^{8,35}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:247)

Example 205: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:248)

Example 206: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:249)

Example 207: (Aib^{8,35}, Arg^{26}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:250)

Example 208: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:251)

Example 209: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:252)

Example 210: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:253)

Example 211: (Aib^{8,35}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:254)

Example 212: (Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:255)

Example 213: (Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:256)

Example 214: (Aib^{8,24,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:257)

Example 215: (Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:258)

Example 216: (Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:259)

Example 217: (Aib^{8,24,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:260)

Example 218: (Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:261)

Example 219: (Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:262)

Example 220: (Aib^{8,24,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:263)

Example 221: (Aib^{8,24,35}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:264)

Example 222: (Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:265)

Example 223: (Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:266)

Example 224: (Aib^{8,35}, Glu^{23}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:267)

Example 225: (Aib^{8,35}, Glu^{23}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:268)

Example 226: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{34}(N$_{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:269)

Example 227: (Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:270)

Example 228: (Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:271)

Example 229: (Aib^{8,35}, Glu^{23}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:272)

Example 230: (Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:273)

Example 231: (Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:274)

Example 232: (Aib^{8,35}, Glu^{23}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:275)

Example 233: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:276)

Example 234: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:277)

Example 235: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:278)

Example 236: (Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-octanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:279)

Example 237: (Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-tetradecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:280)

Example 238: (Aib^{8,30,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanoyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:281)

Example 239: (Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:282)

Example 240: (Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:283)

Example 241: (Aib^{8,30,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:284)

Example 242: (Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:285)

Example 243: (Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:286)

Example 244: (Aib^{8,30,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:287)

Example 245: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:288)

Example 246: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:289)

Example 247: (Aib^{8,35}, Glu^{23}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:290)

Example 248: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:291)

Example 249: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:292)

Example 250: (Aib^{8,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:293)

Example 251: (Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:294)

Example 252: (Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:295)

Example 253: (Aib^{8,24,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:296)

Example 254: (Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:297)

Example 255: (Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:298)

Example 256: (Aib^{8,24,30,35}, Glu^{23}, Arg^{26,34}, A6c^{32}, Lys^{36}(N$^{\varepsilon}$-hexadecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:299)

Example 257: ((N$^{\alpha}$-HEPES-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:300)

Example 258: ((N$^{\alpha}$-HEPES-His)^{7}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:301)

Example 259: ((N$^{\alpha}$-HEPES-His)^{7}, Aib^{8}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:302)

Example 260: ((N$^{\alpha}$-HEPA-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:303)

Example 261: ((N$^{\alpha}$-HEPA-His)^{7}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:304)

Example 262: ((N$^{\alpha}$-HEPA-His)^{7}, Aib^{8}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:305)

Example 263: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:306)

Example 264: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:307)

Example 265: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:308)

Example 266: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:309)

Example 267: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{26,34}, Aib^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:310)

Example 268: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{26,34}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:311)

Example 269: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:312)

Example 270: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, Arg^{26,34}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:313)

Example 271: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Arg^{25,26,34}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:314)

Example 272: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:315)

Example 273: ((N$^{\alpha}$-tetradecanoyl-His)^{7}, Aib^{8}, Arg^{25,26,34}, β-Ala^{35})hGLP-1(7-36)NH$_2$ (SEQ ID NO:316)

Example 274: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-octanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:317)

Example 275: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-dodecanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:318)

Example 276: (Aib^{8,35}, Lys^{26}(N$^{\varepsilon}$-hexadecanesulfonyl), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:319)

Example 277: (Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-octanesulfonyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:320)

Example 278: (Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-dodecanesulfonyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:321)

Example 279: (Aib^{8,35}, Arg^{26}, Lys^{34}(N$^{\varepsilon}$-hexadecanesulfonyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:322)

Example 280: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-octanesulfonyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:323)

Example 281: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-hexadecanesulfonyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:324)

Example 282: (Aib^{8,35}, Asp^{26}(1-(4-decylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:325)

Example 283: (Aib^{8,35}, Asp^{26}(1-(4-dodecylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:326)

Example 284: (Aib^{8,35}, Asp^{26}(1-(4-tetradecylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:327)

Example 285: (Aib^{8,35}, Asp^{26}(1-(4-hexadecylpiperazine)), Arg^{34})hGLP-1(7-36)NH$_2$ (SEQ ID NO:328)

Example 286: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-decylpiperazine)))hGLP-1(7-36)NH$_2$ (SEQ ID NO:329)

Example 287: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH$_2$ (SEQ ID NO:330)

Example 288: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH$_2$ (SEQ ID NO:331)

Example 289: (Aib^{8,35}, Arg^{26}, Asp^{34}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:332)

Example 290: (Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:333)

Example 291: (Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:334)

Example 292: (Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:335)

Example 293: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:336)

Example 294: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:337)

Example 295: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:338)

Example 296: (Aib^{8,35}, Arg^{26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:339)

Example 297: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:340)

Example 298: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:341)

Example 299: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:342)

Example 300: (Aib^{8,35,37}, Arg^{26,34}, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:343)

Example 301: (Aib^{8,35,} , Arg^{25,34}, Asp^{26}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:344)

Example 302: (Aib^{8,35,} , Arg^{25,34}, Asp^{26}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:345)

Example 303: (Aib^{8,35}, Arg^{25,34}, Asp^{26}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:346)

Example 304: ($Aib^{8,35,}$, $Arg^{25,34}$, Asp^{26}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:347)

Example 305: ($Aib^{8,35}$, $Arg^{25,26}$, Asp^{34}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:348)

Example 306: ($Aib^{8,35}$, $Arg^{25,26}$, Asp^{34}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:349)

Example 307: ($Aib^{8,35}$, $Arg^{25,26}$, Asp^{34}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:350)

Example 308: ($Aib^{8,35}$, $Arg^{25,26}$, Asp^{34}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:351)

Example 309: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{36}(1-(4-decylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:352)

Example 310: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{36}(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:353)

Example 311: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{36}(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:354)

Example 312: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{36}(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH_2 (SEQ ID NO:355)

Example 313: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:356)

Example 314: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:357)

Example 315: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:358)

Example 316: ($Aib^{8,35}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:359)

Example 317: ($Aib^{8,35,37}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-decylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:360)

Example 318: ($Aib^{8,35,37}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:361)

Example 319: ($Aib^{8,35,37}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:362)

Example 320: ($Aib^{8,35,37}$, $Arg^{25,26,34}$, Asp^{38}(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH_2 (SEQ ID NO:363)

Example 321: ($Aib^{8,35}$, $Arg^{26,34}$, Glu^{36}(1-dodecylamino))hGLP-1(7-36)NH_2 (SEQ ID NO:364)

Example 322: ($Aib^{8,35}$, Glu^{26}(1-dodecylamino), Arg^{34})hGLP-1(7-36)NH_2 (SEQ ID NO:365)

Example 323: ($Aib^{8,35}$, $Arg^{26,}$, Glu^{34}(1-dodecylamino))hGLP-1(7-36)NH_2 (SEQ ID NO:366)

Example 324: ($Aib^{8,35,37}$, $Arg^{26,34}$, Glu^{38}(1-dodecylamino))hGLP-1(7-38)NH_2 (SEQ ID NO:367)

Example 325: ($Aib^{8,35}$, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:368)

Example 326: ($Aib^{8,35}$, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:369)

Example 327: ($Aib^{8,35}$, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:370

Example 328: ($Aib^{8,35}$, Arg^{34}, Lys^{26}(N^{ε}-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:371)

Example 329: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:372)

Example 330: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:373)

Example 331: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:374)

Example 332: ($Aib^{8,35}$, Arg^{26}, Lys^{34}(N^{ε}-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:375)

Example 333: ($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N^{ε}-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:376)

Example 334: ($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N^{ε}-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:377)

Example 335: ($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N^{ε}-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:378)

Example 336: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:379)

Example 337: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:380)

Example 338: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:381)

Example 339: (Aib^{8,35}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:382)

Example 340: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:383)

Example 341: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:384)

Example 342: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:385)

Example 343: (Aib^{8,35,37}, Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:386)

Example 344: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:387)

Example 345: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:388)

Example 346: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:389)

Example 347: (Aib^{8,35}, Arg^{25,34}, Lys^{26}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:390)

Example 348: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:391)

Example 349: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:392)

Example 350: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:393)

Example 351: (Aib^{8,35}, Arg^{25,26}, Lys^{34}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:394)

Example 352: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:395)

Example 353: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:396)

Example 354: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:397)

Example 355: (Aib^{8,35}, Arg^{25,26,34}, Lys^{36}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2 (SEQ ID NO:398)

Example 356: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:399)

Example 357: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:400)

Example 358: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:401)

Example 359: (Aib^{8,35}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:402)

Example 360: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:403)

Example 361: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:404)

Example 362: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:405)

Example 363: (Aib^{8,35,37}, Arg^{25,26,34}, Lys^{38}(N$^{\varepsilon}$-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH_2 (SEQ ID NO:406)

Example 364: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH (SEQ ID NO:407)

Example 365: (Aib^{8,35}, Lys^{25}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)OH (SEQ ID NO:408)

Example 370: (Aib^{8,35}, Arg^{26,34}, Ava^{37}, Ado^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:409)

Example 371: (Aib^{8,35}, Arg^{26,34}, Asp^{37}, Ava^{38}, Ado^{39})hGLP-1(7-39)NH_2 (SEQ ID NO:27)

Example 372: (Aib^{8,35}, Arg^{26,34}, Aun^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:28)

Example 373: (Aib^{8,17,35})hGLP-1(7-36)NH_2 (SEQ ID NO:29)

Example 374: (Aib^{8}, Arg^{26,34}, β-Ala^{35}, D-Asp^{37},Ava^{38}, Aun^{39})hGLP-1(7-39)NH_2 (SEQ ID NO:30)

Example 375: (Gly^{8}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:31)

Example 376: (Ser^{8}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:32)

Example 377: (Aib^{8}, Glu^{22,23}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:33)

Example 378: (Gly^{8}, Aib^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:34)

Example 379: (Aib^{8}, Lys^{18}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO: 35)

Example 380: (Aib^{8}, Leu^{27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:36)

Example 381: (Aib^{8}, Lys^{33}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:37)

Example 382: (Aib^{8}, Lys^{18}, Leu^{27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:38)

Example 383: (Aib^{8}, D-Arg^{36})hGLP-1(7-36)NH_2 (SEQ ID NO:39)

Example 384: (Aib^{8}, β-Ala^{35}, D-Arg^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:40)

Example 385: (Aib^{8,27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:41)

Example 386: (Aib^{8,27}, β-Ala^{35,37}, Arg^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:42)

Example 387: (Aib^{8,27}, β-Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH_2 (SEQ ID NO:43)

Example 388: (Aib^{8}, Lys^{18,27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:44)

Example 389: (Aib^{8}, Lys^{27}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:45)

Example 390: (Aib^{8}, β-Ala^{35}, Arg^{38})hGLP-1(7-38)NH_2 (SEQ ID NO:46)

Example 391: (Aib^{8}, Arg^{26,34}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:47)

Example 392: (Aib^{8}, D-Arg^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:48)

Example 393: (Aib^{8}, β-Ala^{35}, Arg^{37})hGLP-1(7-37)NH_2 (SEQ ID NO:49)

Example 394: (Aib^{8}, Phe^{31}, β-Ala^{35})hGLP-1(7-36)NH_2 (SEQ ID NO:50)

Example 395: (Aib^{8,35}, Phe^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:51)

Example 396: (Aib^{8,35}, Nal^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:52)

Example 397: (Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH_2 (SEQ ID NO:53)

Example 398: (Aib^{8,35}, Arg^{26,34}, Nal^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:54)

Example 399: (Aib^{8,35}, Arg^{26,34}, Phe^{31})hGLP-1(7-36)NH_2 (SEQ ID NO:55)

Example 400: (Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH_2 (SEQ ID NO:56)

Example 401: (Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH_2 (SEQ ID NO:57)

Example 402: (Aib^{8,35}, Lys^{36}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH_2 (SEQ ID NO:58)

Example 403: (Aib^{8,35}, Arg^{34}, Lys^{26}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:59)

Example 404: (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(7-36)NH$_2$ (SEQ ID NO:60)

Example 405: (Aib^{8}, β-Ala^{35}, Ser^{37}(O-decanoyl))hGLP-1(7-37)NH$_2$ (SEQ ID NO:61)

Example 406: (Aib^{8,27}, β-Ala^{35,37}, Arg^{38}, Lys^{39}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-39)NH$_2$ (SEQ ID NO:62)

Example 407: (Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-octanoyl))hGLP-1(7-37)NH$_2$ (SEQ ID NO:63)

Example 408: (Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-decanoyl))hGLP-1(7-37)NH$_2$ (SEQ ID NO:64)

Example 409: (Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-37)NH$_2$ (SEQ ID NO:65)

Example 410: (Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(7-37)NH$_2$ (SEQ ID NO:410)

Example 411: (Aib^{8}, Arg^{26,34}, β-Ala^{35}, Lys^{37}(N$^{\varepsilon}$-dodecanoyl))hGLP-1(8-37)NH$_2$ (SEQ ID NO:411)

Physical data for a representative sampling of the compounds exemplified herein are given in Table 1.

TABLE 1:

Example Number	Mol. Wt. Expected	Mol. Wt. MS(ES)	Purity (HPLC)
24	3351.8	3352.2	88%
26	3340.17	3340.9	99%
27	3353.81	3353.9	99%
29	3353.81	3353.9	99%
45	3352.6	3352.5	97%
51	3326.74	3326.6	99%
78	3395.81	3395.5	96%
136	3494	3494	99%
364	3523.02	3523.6	99%
365	3580.13	3580.3	95%
369	3677.25	3677	97%
370	3692.28	3692.4	98%
371	3807.37	3807.3	98%
372	3579.11	3579.7	97.90%
373	3337.81	3338.5	94%
374	3779.3	3779.5	94%
375	3297.7	3297.5	99%
376	3327.7	3327.4	98%
377	3398.8	3398.7	97.50%

378	3311.6	3311	93%
379	3366.85	3366.5	97%
380	3309.8	3309.4	99%
381	3354.8	3354.5	97.70%
382	3350.9	3350.3	97.20%
383	3311.73	3310.7	92%
384	3481.95	3481.3	94.30%
385	3281.76	3281.6	98%
386	3509.02	3509.1	99.40%
387	3665.2	3665.1	99%
388	3365.91	3365	97%
389	3324.79	3324.2	95%
390	3539	3539.2	93%
391	3381.74	3381.3	97%
392	3410.89	3409.8	99%
393	3481.95	3481.1	90%
394	3286.76	3286.2	99.20%
395	3300.76	3299.4	93%
396	3350.81	3349.4	99%
397	3400.87	3400.1	99%
398	3406.84	3406.4	99%
399	3356.77	3356.6	99%
400	3384.87	3384.43	94%
401	3400.87	3401.3	99%
402	3466.03	3466.9	97.40%
403	3522.05	3522.06	93%
404	3550.11	3550.2	98%
405	3567.09		99%
406	3763.38	3763.2	95%
407	3636.15	3635.8	99%
408	3664.21	3663.3	99%
409	3720.32	3719.5	99%
410	3692.27	3691.7	99%
411	3555.13	3554.4	99%